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IN THE UNITED STATES PATENT & TRADEMARK OFFICE

IN RE APPLICATION OF :  
HIROTOSHI ISHIDA, ET AL. : EXAMINER: TRAN LIEN, THUY  
SERIAL NO: 10/722,679 and 90/007,160 :  
FILED: NOVEMBER 28, 2003 : GROUP ART UNIT: 1761  
FOR: SWEETENER COMPOSITION :

INFORMATION DISCLOSURE STATEMENT UNDER 37 CFR 1.97

COMMISSIONER FOR PATENTS  
ALEXANDRIA, VIRGINIA 22313

SIR:

Pursuant to 37 C.F.R. §1.56 and 37 C.F.R. §1.97, Applicants wish to make of record the following information:

Applicants undertook testing to confirm if pure C-type crystal of N-[N-(3,3-dimethylbutyl)-L- $\alpha$ -aspartyl]-L-phenylalanine 1-methyl ester (“DMB-APM” or “neotame”) is obtained by the conditions described in U.S. Patent No. 5,480,668, as described at col. 7, lines 24-51, or in U.S. Patent No. 5,728,862, as described at col. 4, lines 32-49.

Preparation of Test Samples

**(1) Run 1:** A methanol/water solvent according to U. S. Patent 5,728,862 (17-25% aqueous methanol solution) was prepared by mixing 30.05 g of methanol and 105.17 g of water. Thereafter, 6.41 g of DMB-APM (NutraSweet Co.’s Neotame lot # D106023325) was added to 49.92 g of the solvent and dissolved completely by heating to 60°C. The amount of DMB-APM was determined according to the preliminary test to study the amounts in which crystals

were obtained when cooled down to 10°C. The cooling crystallization according to U.S. Patent 5,728,862 was carried out at 10-15°C for 2 to 12 hours. The solution was cooled down from 60 to 10°C at a rate of 10°C per hour and then kept at 10°C for crystallization. The precipitated solid was filtered by suction filtration and dried by vacuum drier (Yamato Scientific Co's DP33) at 40°C for 16 hours. Crystalline sample was obtained.

**(2) Run 2:** An ethanol/water solvent according to U.S. Patent No. 5,480,668 was prepared by mixing 25 ml of ethanol and 25 ml of water. Thereafter, 11.06 g of DMB-APM (NutraSweet Co.'s Neotame lot # D106023325) was added to 30.05 g of the solvent and dissolved completely by heating to 60°C. The amount of DMB-APM was determined according to the preliminary test to study the amounts in which crystals were obtained when cooled down to 10°C. The cooling crystallization was carried out at 10-15°C for 2 to 12 hours, as in U.S. Patent No. 5,728,862. The solution was cooled down from 60 to 10°C at a rate of 10°C per hour and then kept at 10°C for crystallization. The precipitated solid was filtered by suction filtration and dried by vacuum drier (Yamato Scientific Co's DP33) at 40°C for 16 hours. Crystalline sample was obtained.

**(3) Run 3:** Acetonitrile was used as solvent according to U.S. Patent No. 5,480,668. 17.51 g of DMB-APM (NutraSweet Co.'s Neotame lot # D106023325) was added to 20.1 g of acetonitrile and dissolved completely by heating to 60°C. The amount of DMB-APM was determined according to the preliminary test to study the amounts in which crystals were obtained when cooled down to 10°C. The cooling crystallization was carried out at 10-15°C for 2 to 12 hours, as in U.S. Patent No. 5,728,862. The solution was cooled down from 60 to 10°C at a rate of 10°C per hour and then kept at 10°C for crystallization. The precipitated

solid was filtered by suction filtration and dried by vacuum drier (Yamato Scientific Co's DP33) at 40°C for 16 hours. Crystalline sample was obtained.

**(4) Run 4:** A methanol/water solvent according to U.S. Patent No. 5,728,862 (17-25% aqueous methanol solution) was prepared by mixing 30.05 g of methanol and 105.17 g of water. Thereafter, 4.2 g of DMB-APM (NutraSweet Co.'s Neotame lot # D106023325) was added to 20.24 g of the solvent and dissolved completely by heating to 60°C. The amount of DMB-APM was determined according to the preliminary test to study the amounts in which crystals were obtained when cooled down to 10°C. The cooling crystallization was carried out at 10-15°C for 2 to 12 hours, as in U.S. Patent No. 5,728,862. The solution was cooled down from 60 to 10°C at a rate of 10°C per hour and then kept at 10°C for crystallization. The precipitated solid was filtered by suction filtration and dried by vacuum drier (Yamato Scientific Co's DP33) at 40°C for 16 hours. Crystalline sample was obtained.

**(5) Run 5:** An ethanol/water solvent according to U.S. Patent No. 5,480,668 was prepared by mixing 25 ml of ethanol and 25 ml of water. Thereafter, 9.84 g of DMB-APM (NutraSweet Co.'s Neotame lot # D106023325) was added to 20.06 g of the solvent and dissolved completely by heating to 60°C. The amount of DMB-APM was determined according to the preliminary test to study the amounts in which crystals were obtained when cooled down to 10°C. The cooling crystallization was carried out at 10-15°C for 2 to 12 hours, as in U.S. Patent No. 5,728,862. The solution was cooled down from 60 to 10°C at a rate of 10°C per hour and then kept at 10°C for crystallization. The precipitated solid was filtered by suction filtration and dried by vacuum drier (Yamato Scientific Co's DP33) at 40°C for 16 hours. Crystalline sample was obtained.

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**(6) Run 6:** Acetonitrile was used as solvent according to U.S. Patent 5,480,668. 10.47 g of DMB-APM (NutraSweet Co.'s Neotame lot # D106023325) was added to 20.18 g of acetonitrile and dissolved completely by heating to 60°C. The amount of DMB-APM was determined according to the preliminary test to study the amounts in which crystals were obtained when cooled down to 10°C. The cooling crystallization was carried out at 10-15°C for 2 to 12 hours, as in U.S. Patent No. 5,728,862. The solution was cooled down from 60 to 10°C at a rate of 10°C per hour and then kept at 10°C for crystallization. The precipitated solid was filtered by suction filtration and dried by vacuum drier (Yamato Scientific Co's DP33) at 40°C for 16 hours. Crystalline sample was obtained.

### Analyses

Water content of the dried sample was analyzed by Karl-Fischer moisture analyzer MKA-210 (Kyoto Electronics Manufacturing Co. Ltd) and crystal type was analyzed by X ray diffractometer (PANalytical's X'Pert with X'Celerator, Tube:Cu,30mA,40kV,Sampling width: 0.020°,scanning speed :3°/min, wave length:1.54056 Å, 2θ:4-30°).

### Result

The results are shown in Table 1.

Table 1.

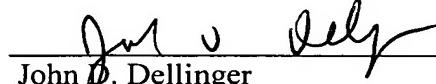
	Solvent	USPatent	Amount of added neotame (g)	Concentration of added neotame (weight %)	Temp. of precipitation (°C)	Time of precipitation (hr:min)	Amount of crystal (g)	Water content (weight %)	Type of crystal
Added neotame	-	-	-	-	-	-	-	5.812	A
Run-1	MeOH:H <sub>2</sub> O	5,728,862	6.41	11.38	18.90	4:12	4.72	0.4083	G
Run-2	EtOH:H <sub>2</sub> O	5,480,668	11.06	26.90	12.44	4:50	6.80	0.184	G
Run-3	MeCN	5,480,668	17.51	46.56	16.78	4:25	16.51	0.1223	A+C
Run-4	MeOH:H <sub>2</sub> O	5,728,862	4.20	17.18	10.10	5:36	4.21	10.144	A+F
Run-5	EtOH:H <sub>2</sub> O	5,480,668	9.84	32.91	10.87	4:58	8.69	3.3418	G
Run-6	MeCN	5,480,668	10.47	34.16	10.00	8:25	3.25	0.2451	A+C

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Applicants respectfully request due consideration of this information.

Respectfully submitted,

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